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Can education rescue genetic liability for cognitive decline?

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ABSTRACT

Although there is a vast literature linking education and later health outcomes, the mechanisms underlying these associations are relatively unknown. In the spirit of some medical literature that leverages developmental abnormalities to understand mechanisms of normative functioning, we explore the ability of higher educational attainments to "rescue" biological/genetic liabilities in brain function through inheritance of a variant of the *APOE* gene shown to lead to cognitive decline, dementia, and Alzheimer's disease in old age. Deploying a between-sibling design that allows quasi-experimental variation in genotype and educational attainment within a standard gene–environment interaction framework, we show evidence that the genetic effects of the "risky" *APOE* variant on old-age cognitive decline are absent in individuals who complete college (vs. high school graduates). Auxiliary analyses suggest that the likely mechanisms of education are most consistent through changing brain processes (i.e., "how we think") and potentially building cognitive reserves, rather than alleviating old age cognitive decline through the channels of higher socioeconomic status and resources over the life course.

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1. Introduction

The impacts of educational attainments on a variety of outcomes over the life course are large and well known. In addition to large increases in material resources (e.g., lifetime income) attributable to higher educational attainment, health status has been shown to be highly associated with education across time periods, across countries, and over the life cycle. More highly educated mothers give birth to healthier babies (Currie and Moretti, 2003) and more highly educated individuals live longer than individuals with lower levels of schooling; for example, the age-adjusted mortality rate of high school dropouts ages 25 to 64 was more than twice as large as the mortality rate of those with some college (Table 26, Cutler and Lleras-Muney, 2006). There is a large literature using changes in compulsory schooling laws in the 1900s to examine impacts of educational attainment on old age mortality. This literature has been quite mixed, with Lleras-Muney (2005) showing some evidence of effects in a US sample, but other studies in European countries showing no impacts. See Fletcher (2013) for a review and new evidence. In between birth and death, more highly educated individuals smoke less (Farrell and Fuchs, 1982; Maralani, 2013), are less likely to be overweight (McLaren, 2007; Cutler and Lleras-Muney, 2010), and are more likely to pursue preventative health care steps (Fletcher and Frisvold, 2009). However, as methods aimed at causal inference have been employed, the evidence linking educational attainment and health status and behaviors has become more mixed (Royer and Clark, 2013).

While there are large literatures examining the impacts of education on health behaviors and health status over time and across countries, the mechanisms underlying these links remain unclear. Indeed, a next step in understanding long term impacts of education on health is in considering specific mechanisms. One dichotomy that might help us understand the extent of key mechanisms is between socioeconomic and biological channels. Education may enhance future health through the acquisition of financial and social resources that are important for maintaining health (e.g., income, health insurance, strong peer networks) and/or it may enhance future health through structuring and restructuring brain development and activity that is helpful for health and wellbeing (see Cutler and Lleras-Muney, 2006 for a review). Both are likely important channels, but the latter has had limited examination, particularly in explorations that have strong causal grounding.

This paper focuses attention on the second, biological, channel while attempting to hold the other channel constant in the context of a specific marker of health: life course brain function atrophy (i.e., cognitive decline). In order to uncover novel evidence of potential mechanisms underlying the relationship of education and

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cognitive function in old age, we focus attention on the well-known differences in trajectories of brain malfunction between individuals with alternative variants of the *APOE* gene. In particular, we ask whether higher educational attainment "rescues" genetic liabilities of cognitive decline in old age by enhancing cognitive reserve. To explore this question, we use unique panel data collected over 50 years, a gene–environment interaction framework and a sibling-difference specification. In doing so, we attempt to go "under the scalp" in examining mechanisms of educational attainment impacts. Indeed, we find evidence that, among college graduates, *APOE* differences do not lead to cognitive decline differences; among high school graduates, *APOE* differences lead to large differences in cognitive decline in old age. These findings do not change when we add potential "social" (i.e., non-biological) mediators, such as wealth, marital status, health insurance, occupation, etc., which is consist with a biological mechanism linking education with cognitive reserve through changes in "how we think".

2. Background

2.1. APOE4

The *APOE* gene is associated with the production of apolipoprotein, which transports cholesterol and other fatty acids within the blood (Bu, 2009). The functional variation in *APOE* is the result of two SNPs, or singular nucleotide polymorphisms: SNP rs429358 and SNP rs7412, with each SNP having two alleles, or genetic variants. Three major functional variants exist for the *APOE* gene: APOE2, APOE3, and APOE4. For European populations, the respective allele distribution is roughly 14%, 72%, and 14% for the three variants (Singh et al., 2006).

The E4 variant, the variant of interest throughout the paper, is strongly associated with late-onset Alzheimer's Disease (LOAD), which occurs between 60 and 70 years of age (Blacker et al., 1997). For meta and genome wide association analyses of the association between LOAD and APOE4 see Corder et al. (1993), Farrer et al. (1997), and Bertram et al. (2007). While roughly 15% of the general population possesses the E4 variant, the frequency rises to roughly 40% in those with Alzheimer's Disease (Corder et al., 1993).

One potential mechanism of APOE's role in LOAD is in the accumulation of amyloid plaques (Bu, 2009). Amyloid precursor proteins are hypothesized to play a role in synapse formation, and the accumulation of a byproduct of this protein, beta amyloid, has strong associations with AD (Blennow et al., 2006; Priller et al., 2006). Compared to the more common E3 variant, the E4 variant of APOE is less efficient at removing beta amyloid, leading to a greater accumulation of harmful amyloid plaques (Bu, 2009). A number of mouse studies confirm the poor clearance of E4 for the beta amyloid peptide; see e.g., Holtzman et al. (1999, 2000), and DeMattos et al. (2004).

The timing of the impacts of the E4 variant is important. Because the less efficient polymorphism allows the greater accumulation of plaques over the life course, the impacts of having the "risk" allele are not apparent until old age. Specifically, this means that educational attainments and cognitive function during adolescence and young adulthood are likely not to be impacted. Like many other studies, we show this in our data—individuals with the E4 variant have the same IQ at age 17 and have the same educational attainments as individuals with an alternative variant. This is consistent with evidence from Ilhe et al. (2012), from which the authors find no association between the harmful E4 variant and early-life cognitive function. The accumulation of amyloid plaques, which is associated with later-life loss of cognitive function, occurs throughout the life-course and materializes in the late-onset period of 60–70 years of age. The accumulation of beta amyloid is hypothesized to affect cognition 2–3 decades prior to the onset of AD, a time after the formal education period (Davies et al., 1988; Villemagne et al., 2013). This particular timing of effects of the E4 variant over the life course can allow a unique lens in understanding the role of education in cognitive function and decline, as well as assessing causality that have not been exploited for these purposes in the literature. In order to pursue these questions, we take advantage of the emerging gene–environment interaction framework.

2.2. Gene–environment interaction

A growing literature is focused on the differential response to environmental stimuli based on underlying genetic differences within individuals. These interactions between genes and environment provide evidence for the moderating, or amplifying, influence of certain genetic variants in explaining heterogeneity in health, cognitive, and economic outcomes from exposure to harmful or beneficial environments (for review see Caspi and Moffitt, 2006). An alternative view of this research is to focus on the moderating influence of environmental exposures to a harmful genetic variant, which are strongly associated with an observed, or phenotypic, outcome. In other words, the negative outcomes, which are the result of genetic endowments determined at conception, can be reversed by exposure to particular environments. With this idea in mind, we focus on the role of *APOE4* in explaining declines in later-life cognition.

As discussed above, Late-onset Alzheimer's Disease (AD), which typically occurs between 60 and 70 years of age, is strongly associated with the E4 variant of the apolipoprotein-E (*APOE*) gene (Rhinn et al., 2013). This association is one of the most widely recognized and replicated instances of a singular genetic change being associated with an observed behavior, or phenotype (see e.g., Bertram et al., 2007 for meta-analysis and the resulting AlzGene database). Individuals with two copies of the E4 variant have been shown to be 7 times more likely to develop AD than those with the more common E3 variant (Corder et al., 1993). The association between *APOE4* and cognition does not exist, however, early in life, suggesting that any beneficial environmental experiences are unlikely to be driven by genetic variation in *APOE* (Ilhe et al., 2012). This is important from a research design perspective, as gene-environment correlation ("genes selecting environments") can challenge attempts at estimating causal impacts of gene–environment interactions (Fletcher and Conley, 2013).

Towards this end, we propose that formal education serves as a moderating factor in the expression of the E4 variant for later-life declines in cognition. Physiologically, years of schooling has been shown to increase the volume and metabolism of gray matter while also strengthening neurological connections (Arenaza-Urquijo et al., 2013). Additionally, cognitive stimulation in early to mid-life (a time span correlated with the formal education period) has been shown to reduce the accumulation of amyloid-beta deposition in later-life (Landau et al., 2012).

Our proposed hypothesis is that the negative effects of *APOE4* on later-life cognition are offset by increases in education, measured by years of schooling. Years of schooling represents an environmental "shock" (i.e., unrelated to genotype) in early life that has effects on both the physiological development of the brain and in unobserved cognitive processing. Towards this end, we estimate a gene–environment interaction model between the harmful, or cognitively damaging, variant of the *APOE* gene and years of schooling on changes in later-life cognition during the late-onset period of AD. Given this estimation strategy our focus is on the marginal effect of *APOE4* for varied levels of schooling, with the hypothesized effect being a lessened impact of the harmful E4 variant for individuals with increased levels of schooling. Furthermore to lessen potential bias from unobserved environments as well as the unobserved

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